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(54) **Sustained release compositions for treating periodontal disease**

Pharmazeutische Zubereitungen mit verzögerter Freisetzung zur Behandlung periodontaler Erkrankungen

Composition pharmaceutique pour le traitement des maladies périodontales à libération prolongée

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## Description

This invention relates to compositions/devices for treating diseases of the oral cavity, which compositions/devices are placed in or around the periodontal pocket. The invention also relates to methods of using the compositions/devices in humans and lower animals suffering from such diseases.

Periodontal disease, for example, is a major cause of tooth loss in adults. Tooth loss from periodontal disease is a significant problem beginning at age 35, but even by age 15 it is estimated that about 4 out of 5 persons already have gingivitis and 4 out of 10 have periodontitis.

While good oral hygiene, as achieved by brushing the teeth with a cleansing dentifrice, may help reduce the incidence of periodontal disease, it does not necessarily prevent or eliminate its occurrence. This is because microorganisms contribute to both the initiation and progress of periodontal disease. Thus, in order to prevent or treat periodontal disease, these microorganisms must be suppressed by some means other than simple mechanical scrubbing. Towards this end, there has been a great deal of research aimed at developing therapeutic dentifrices, mouthwashes, and methods of treating periodontal disease which are effective in suppressing these microorganisms.

Recent developments in the art are directed toward delivering the therapeutic agent directly to the periodontal pocket, in some cases in a controlled release formulation. Gordon et al. have described the use of a drug-filled polymer hollow fiber. (J.M. Goodson et al., "Periodontal Therapy by Local Delivery of Tetracycline", J. Clin. Periodontal. 6, 83 (1979), J. Lindhe et al., "Local Tetracycline Delivery Using Hollow Fiber Devices in Periodontal Therapy", J. Clin. Periodontal. 6, 141 (1979) and R.L. Dunn et al., "Monolithic Fibers for Controlled Delivery of Tetracycline", in Proc. Ninth Int. Symposium on Controlled Release of Bioactive Materials, Ft. Lauderdale, FL, July (1982). This device is tied around a tooth and gently pressed below the margin of the gingiva so that it resides in the periodontal pocket, and is capable of delivering an effective dose of 2.5 micrograms of tetracycline per day per periodontal pocket for a prolonged period of a week or more. Similar results have been obtained by Coventry and Newman (J. Coventry and H. N. Newman, "Experimental Use of a Slow Release Device Employing Chlorhexidine Gluconate in Areas of Acute Periodontal Inflammation", J. Clin. Periodontal. 9, 129 (1982) and Addy et al. (M. Addy et al., "The Development and in vitro Evaluation of Acrylic Strips and Dialysis Tubing for Local Drug Delivery", J. Periodontal 53, 693 (1982) using acrylic strips 1mm or more long, impregnated with chlorhexidine, tetracycline or metronidazole, which were inserted into the periodontal pocket with tweezers. Such a strip, formed from ethylcellulose impregnated with metronidazole, is disclosed by Loesche in US-A-4,568,538 (February 1986). Another strip, employing a water soluble polymer of a particular elasticity and viscosity, is disclosed by Suzuki et al. in US-A-4,569,837.

In addition to the above approaches, the prior art also discloses using putty-like compositions containing an antimicrobial for insertion into the periodontal pocket. See US-A-4,650,665, March 17, 1987 to Kronenthal et al.

The present inventor has discovered that using polypropenoic acid as the material forming the composition/device allows for efficient/good devices to be formed.

Previous attempts to effectively treat periodontal pockets have not been desirably successful. This is largely due to the fact that a periodontal pocket cavity is very narrow and convoluted or tortuous, making it nearly impossible to fill the entire cavity with a treatment product.

This invention, utilizing highly swellable polymer eliminates such problems. Once a product of this invention is placed in periodontal cavity, the polymer swells, expands, and reaches narrow crevices and furcations of the treated cavity, carrying active agent throughout the cavity. This provides most desirable efficacy at treatment site.

It is therefore an object of the present invention to provide polypropenoic compositions/devices suitable for treating periodontal disease and other diseases of the oral cavity.

It is a further object of the present invention to provide such compositions/devices using mixtures of polypropenoic acid and other polymers.

It is still a further object of the present invention to provide a method of treating periodontal disease.

All percentages and ratios used in here are by weight unless otherwise indicated.

All measurements are made at 25°C unless otherwise indicated.

According to the present invention there is provided a composition for insertion into or around the periodontal pocket of a person or lower animal suffering from diseases of the oral cavity comprising a mixture of polypropenoic acid crosslinked with 0.004 mole percent of trimethylpropane triacrylate, a drug active and an additional polymer selected from polycaprolactone and polylactide polymers.

The essential as well as optional components of the compositions/devices of this invention are described below.

### Polymer

The polymer used in the present compositions is referred as super absorbent polymer and is defined as polypropenoic acid, crosslinked with 0.004 mole percent of trimethylpropane triacrylate. This material is provided as Dry Tech 512 by Dow Chemical Company.

The carboxylic groups can be neutralized with, for example, a sodium base to an extent of 75% or more.

A most preferred polymer useful in the present invention has very high, nearly infinite molecular weight in its crosslinked form which is estimated to be 2 million to 10 million or even higher. Unit segments of crosslinked polymer have a range of number average molecular weight from 50,000 to 1 million. The polymer is used in the present compositions at a level of from 1% to 99%, preferably from 10% to 75%, most preferably from 20% to 50%.

Drug Active

The drugs useful for use in the present compositions/devices are varied and many and include any agent which provides treatment of the disease. Some therapeutic agents which are amenable to delivery by this means and are potentially of value for periodontal therapy, include (but are not limited to) antimicrobial/antibacterial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin, metronidazole, or clindamycin; antiinflammatory agents such as aspirin, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamasole; dentinal desensitizing agents such as strontium chloride or sodium fluoride; odor masking agents such as peppermint oil or chlorphyll; immune reagents such as immunoglobulin or antigens; local anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids, essential fats, and vitamin C; antioxidants such as alphatocopherol and butylated hydroxy toluene; lipopolysaccharide complexing agents such as polymyxin; or peroxides such as urea peroxide. It is recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus, for example, an antibacterial and an antiinflammatory agent may be combined in a single delivery system to provide combined effectiveness.

The drug active is used at a level of from 1% to 99%, preferably from 5% to 75%, most preferably from 10% to 50% of the compositions/devices. The compositions/devices, for example, are designed to release drug at a rate to provide concentration of from 10µg to 2000µg, preferably from 50µg to 1000µg, most preferably from 100µg to 500µg per milliliter of the gingival crevicular fluid of a treated periodontal pocket. Desired release rates can be achieved by altering ratios of components in a composition.

In addition to the drug active, the compositions/devices of the present invention say include a variety of optional components. Such components include, but are not limited to, surfactants, viscosity controlling agents, complexing agents, antioxidants, gums such as guar gum, waxes/oils such as caster wax, castor oil, glycerol, dibutyl phthalate and ethyl sebacate as well as many others.

The additional polymer for use herein is selected from polycaprolactone and polylactide. A particularly preferred polymer is a copolymer of lactide and glycolide. Lactide monomeric species preferably comprise 15% to about 85%, most preferably from about 35% to about 65%, of the polymers while glycolide monomers comprise from about 15% to about 85% of the polymer, preferably from about 35% to about 65% on a molar basis. The molecular night lies in the range of from about 1000 to about 120,000 (number average). These polymers are described in detail in US-A-4,443,430, April 17, 1984, to Mattei.

If used, these optional components comprise from about 0.1% to about 50%, preferably from about 0.5% to about 25% of the total composition/device.

Method of manufacturing the compositions/devices of this invention are disclosed in the Examples.

EXAMPLE I

The following is an exemplary composition/device of the present invention.

| | Weight % |
|---|---|
| Tetracycline hydrochloride | 50 |
| Polypropenoic acid | 22.7 |
| Poly(lactyl-co-glycolide)/50:50 copolymer | 22.7 |
| Propylene Carbonate | 4.6 |

The above composition can be prepared in a number of different ways. One way is as follows: Polymer is charged into 110°C, electrically heated mixer, equipped with high shear Sigma type rotor blades. Propylene carbonate is added and mixed into the polymer. The drug is added and mixed until uniform. The drug polymer blend is removed for further processing into desired size and shaped devices.

The compositions/devices of the invention of this application are inserted into or around the periodontal pocket or gingival region, and are administered in the form of a particle, film or sheet. The size, shape, and thickness can be changed according to the condition of the periodontal disease to be treated and they are not particularly critical. Ordinarily, the size, shape, and thickness are changed according to the size of the periodontal pocket of the patient or the condition of the gingiva. The devices may be for example of a size such that the thickness is in the range of 0.01 to 2mm, preferably from about 0.1 to about 1mm; the width in the range of 0.1 to about 5mm, preferably from about 0.2 to about 4mm; and the length in the range of from about 1 to about 15mm, preferably from about 3 to about 10mm.

EXAMPLE II

Given below is still another composition/device representative of the present invention:

| | Wt. % |
|---|---|
| Metronidazole | 40 |
| Polypropenoic acid | 30 |
| Polycaprolactone | 25 |
| Pluronic F-68 | 5 |

EXAMPLE III

Given below is still another composition representative of the present invention:

| | Wt. % |
|---|---|
| Flurbiprofen | 20 |
| Polypropenoic acid | 25 |
| Xanthan Gum | 20 |
| Polylactide polymer | 25 |
| Polyethylene glycol | 10 |

**Claims**

1. A composition for insertion into or around the periodontal pocket of a person or lower animal suffering from diseases of the oral cavity comprising a mixture of polypropenoic acid crosslinked with 0.004 mole percent of trimethylpropane triacrylate, a drug active and an additional polymer selected from polycaprolactone and polylactide polymers.

2. A composition according to Claim 1 wherein the number average molecular weight of individual polypropenoic acid units is from 50,000 to 1 million, which are crosslinked to provide nearly infinite molecular weight.

3. A composition according to Claim 1 or 2 wherein the drug active is selected from antiinflammatory agents, antibiotics, peroxides, anesthetic agents and vitamins.

4. A composition according to any of Claims 1-3 wherein the concentration of drug active is from 5% to 75% by weight.

5. A composition according to any of Claims 1-4 wherein the concentration of the drug active is from 10% to 50% by weight and the active is selected from the tetracycline group of antibiotics.

6. A composition according to any of Claims 1-5 wherein said additional polymer is a copolymer of glycolide and lactide.

## Patentansprüche

1. Zusammensetzung zum Einführen in die Zahnfleischtasche oder zum Anbringen um dieselbe herum, bei einer Person oder einem niedrigeren Tier, welche bzw. welches an Erkrankungen der Mundhöhle leidet, welche Zusammensetzung ein Gemisch aus Polypropensäure, die mit 0,004 Mol-% Trimethylpropantriacrylat vernetzt ist, einem Arzneimittelwirkstoff und einem zusätzlichen, aus Polycaprolacton- und Polylactidpolymeren ausgewählten Polymer umfaßt.

2. Zusammensetzung nach Anspruch 1, wobei das Zahlenmittel-Molekulargewicht der einzelnen Polypropensäureeinheiten 50.000 bis 1 Million beträgt, welche Einheiten unter Bildung eines nahezu unbegrenzten Molekulargewichtes vernetzt sind.

3. Zusammensetzung nach Anspruch 1 oder 2, wobei der Arzneimittelwirkstoff aus entzündungshemmenden Mitteln, Antibiotika, Peroxiden, Anästhetika und Vitaminen ausgewählt ist.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei die Konzentration des Arzneimittelwirkstoffes 5 Gew.-% bis 75 Gew.-% beträgt.

5. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei die Konzentration des Arzneimittelwirkstoffes 10 Gew.-% bis 50 Gew.-% beträgt und wobei der Wirkstoff aus der Tetracyclingruppe von Antibiotika ausgewählt ist.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, wobei das zusätzliche Polymer ein Copolymer aus Glycolid und Lactid ist.

## Revendications

1. Composition à insérer dans ou autour de la poche périodontique d'une personne ou d'un animal inférieur souffrant de maladies de la cavité buccale comprenant un mélange d'acide polypropénoïque réticulé avec 0,004% en mole de triacrylate de triméthylpropane, un principe actif et un polymère supplémentaire choisi parmi la polycaprolactone et les polymères de type polylactide.

2. Composition selon la revendication 1, dans laquelle la masse moléculaire moyenne en nombre des motifs d'acide polypropenoïque individuels est de 50 000 à 1 million, qui sont réticulés pour fournir une masse moléculaire presque infinie.

3. Composition selon la revendication 1 ou 2, dans laquelle le principe actif est choisi parmi les agents anti-inflammatoires, les antibiotiques, les peroxydes, les agents anesthésiants et les vitamines.

4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle la concentration en principe actif est de 5% à 75% en poids.

5. Composition selon l'une quelconque des revendications 1 à 4, dans laquelle la concentration en principe actif est de 10% à 50% en poids et le produit actif est choisi dans le groupe des tétracyclines des antibiotiques.

6. Composition selon l'une quelconque des revendications 1 à 5, dans laquelle ledit polymère supplémentaire est un copolymère de glycolide et de lactide.